DATA EVALUATION RECORD

TRIFLUMEZOPYRIM

STUDY TYPE: SUBCHRONIC TOXICITY – DOG
(OCSPP 870.3150)

MRID 49382159

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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DATA EVALUATION RECORD[1]

STUDY TYPE: Subchronic Toxicity [oral] -Dog;
OCSPP 870.3150 [§82-1] (non-rodent); OECD 409.

PC CODE: 129210 **DP BARCODE:** D432127

TEST MATERIAL (PURITY): DPX-RAB55 (Triflumezopyrim technical; 98.8% a.i.)

SYNONYMS: 2,4-Dioxo-1-(5-pyrmidinylmethyl)-3-[3-(trifluoromethyl)phenyl-2*H*-pyrido [1,2-α]pyrimidium, inner salt

CITATION: Papagiannis, C. (2013) DPX-RAB55 technical: A 28-day oral toxicity/palatability study in dogs. MPI Research, Inc. (Mattawan, Michigan). Laboratory Project No.: DuPont-33755, March 8, 2013. MRID 49382159. Unpublished.

SPONSOR: E. I. du Pont de Nemours and Company (Wilmington, Delaware).

EXECUTIVE SUMMARY: In a 28-day feeding study (MRID 49382159), triflumezopyrim (98.8% a.i., DPX-RAB55) was administered to 2 beagle dogs/sex/dose in diet at concentration levels of 0, 300, 3000, or 30000/15000/10000 ppm (equivalent to a mean daily intake of 0, 6.08, 49.52, or 55.10 mg/kg bw/day, respectively, for males and 0, 8.18, 67.07, or 145.04 mg/kg bw/day, respectively, for females). For the high dose group, the animals received 30000 ppm for Week 1, 15000 ppm for Week 2, and 10000 ppm for Weeks 3 and 4. The dietary concentration was decreased due to low food consumption and severe body weight loss.

All animals survived until their scheduled termination, with the exception of one male from the 10000 ppm group that was found moribund and was euthanized on Day 24. The cause of death was attributed to bacterial pneumonia. Clinical and neurobehavioral observations were noted for males and females at 10000 ppm (55.10/145.04 mg/kg/day [M/F]) and appeared to be associated with the decreased absolute body weights observed in both sexes at this dose.

There were no treatment-related effects on ophthalmoscopy, hematology, coagulation parameters, or urinalysis parameters at doses up to 3000 ppm (49.52/67.07 mg/kg/day [M/F]). For both sexes, there were mild increases in alanine aminotransferase (ALT) and bile acids and

[1] This DER was generated by modifying the study summary in a Tier II document (MRID 49382105).

decreases in total protein and albumin at 10000 ppm (55.10/145.04 mg/kg/day [M/F]). There were no treatment-related changes in organ weights, gross and microscopic pathology, or signs of specific target organ toxicity.

The NOAEL is 3000 ppm (equivalent to 49.52/67.07 mg/kg/day [M/F]). The LOAEL for triflumezopyrim is established at 10000 ppm (equivalent to 55.10/145.04 mg/kg/day [M/F]) based on reductions in absolute body weight.

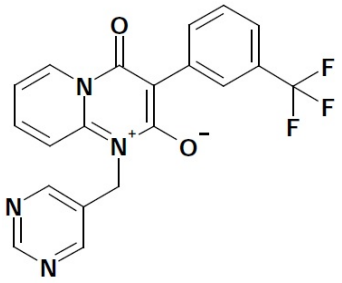
This 28-day oral toxicity study in the dogs is a range-finding study that was conducted for the purpose of setting doses for the follow-on studies. It **does not satisfy** any guideline requirements.

COMPLIANCE: Signed and dated GLP, and Quality Assurance statements were provided. No data confidentiality claim was made as the information in the study was not designated to be within the scope of FIFRA Sec. 10(d) (1) (A), (B), or (C).

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Triflumezopyrim technical

Description:	Dark yellow powder
Batch/Lot #:	SG0311387
Purity:	98.8% a.i.
Compound stability:	Stable at room temperature in diet for 15 days
CAS # of TGAI:	1263133-33-0
Structure:	

2. Vehicle: Basal diet

3. Test animals:

Species:	Dog
Strain:	Beagle
Age/weight at study initiation:	Approximately 9 to 9.5 months old/weight range: 9.21–10.48 kg for males; 8.16–9.08 kg for females
Source:	Marshall BioResources, North Rose, NY
Housing:	Pair-housed (single sex) in runs with raised flooring, except during feeding period and during weekly neurobehavioral examinations when they were singly housed.
Diet:	Lab Diet® (Certified Canine Diet #5007, PMI Nutrition International, Inc.) The untreated or treated canine diet was available once daily (for approximately 2 hours in the morning) for 28 consecutive days. Animals were offered approximately 400 g each day. Several high dose dogs were supplemented with canned food (Hills Prescription Diet p/d) over the last few weeks due to body weight loss.
Water:	Tap water, *ad libitum*
Environmental conditions:	**Temperature:** 64-84°F **Humidity:** 30-70% **Air changes:** Not recorded **Photoperiod:** 12 hrs dark/ 12 hrs light
Acclimation period:	13 days

B. STUDY DESIGN:

1. In life dates: Start: December 14, 2011; End: January 11, 2012

2. Animal assignment: Animals were assigned to dose groups by a standard block randomization procedure based on body weights (females) or testes volume (males) as shown

in Table 1.

Table 1. Study design[a]

Test group	Concentration in diet (ppm)	Mean Daily Intake (mg/kg bw/day)		Males	Females
		Male	Female		
Control (1)	0	0	0	2	2
2	300	6.08	8.18	2	2
3	3000	49.52	67.07	2	2
4	10000[b]	55.10	145.04	2	2

[a] Data obtained from page 129 of MRID 49382105
[b] The dose level was reduced from 30000 ppm to 15000 ppm for Week 2 and reduced to 10000 ppm for Weeks 3 and 4 to reflect changes in bodyweight and maintain a constant bodily dose.

3. **Dose selection rationale/Administration:** This was the first study in which dogs were exposed to the test article. The dietary concentrations were selected based on data from previous studies feeding studies in rodents, in which effects were observed in both rats and mice dosed at limit dose concentrations (equivalent to approximately 1000 mg/kg/day). Therefore, the high dietary concentration was selected to deliver a dose below 1000 mg/kg/day. The mid-concentration was selected to identify a dose-response for any effects observed at the high concentration, and the low concentration is expected to be a NOAEL.

4. **Dose preparation and analysis:** The test substance was added to the diet and thoroughly mixed for approximately 10 and 20 minutes. Control diets were mixed for the same period of time. Samples from the 10-minute mixing interval were initially analyzed. The results of the analysis were satisfactory, therefore, the samples from the 20-minute mixing interval were not analyzed. All diets were prepared weekly and stored at room temperature until used. All analyses were conducted using a validated HPLC method. The homogeneity of the test compound in the dietary mixtures was checked by analysis 10 minutes after mixing (the average recovery range: 94.8%-101.9%; (RSD: 2.166%-9.129%). Concentration of the test compound in the dietary mixtures was analyzed at Weeks 1 and 4 for, 300, 3000, 10000 (Week 4) and 30000 ppm (Week 1). The concentrations were within the expected range of ±10% of the nominal concentration (the average range: 94.5%-102.5%). Stability was evaluated prior to study start as part of the analytical method validation study. MPI Research study number 125-161 (DuPont-19685-395-1; the method validation study) established 15-day room temperature stability for the test diet at concentrations of 300-30000 ppm.

5. **Results:**

Homogeneity analysis: Based on a pretest homogeneity analysis using a blending time of 10 minutes, the relative standard deviation (RSD) for the 300, 3000, or 30000 ppm dose groups were 9.1%, 4.7%, or 2.2%, respectively. All test diets met the acceptance criterion for RSD (≤15%); however, a 20-minute blending time was utilized for the study test diet preparations

to further minimize the variability.

Stability analysis: Confirmed over a period of 15 days at room temperature.

Concentration analysis: Analysis of test formulations conducted over four weeks showed that the mean concentration range for the 300 and 3000 ppm dose groups was 94.5%-99.9% and 96.8%-102.5%, respectively; for 10000 ppm (Week 4) and 30000 ppm (Week 1) the mean concentrations were 99.6% and 99.8%, respectively, of nominal concentrations. The test substance was at ± 10% of the target concentrations.

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable. Based on this information, it can be concluded that the animals received the targeted dietary concentrations of test substance during the study.

6. **Statistics:** The group-wise comparisons of data were not conducted due to small sample size. However, means, standard deviations, and number of animals in each treatment as well as time period, by sex were calculated.

C. METHODS:

1. Observations:

1a. Clinical examinations: Animals were observed twice daily for mortality, morbidity, injury, and the availability of food and water. Detailed clinical examinations were conducted once daily (within 1 hour after removal of food).

1b. Neurological evaluations: Neurobehavioral observations were conducted weekly (approximately 4 hours after food removal) and included examining animals for bizarre behavior or altered appearance and subjected to detailed examinations.

2. **Body weight:** Animals were weighed on the study day 1 (prior to dosing), and weekly thereafter.

3. **Food consumption/Food efficiency/Daily Intake:** Food consumption was recorded daily for each animal, and the mean group food consumption and daily intake of test substance were calculated weekly.

4. **Ophthalmoscopic examination:** Ophthalmological examinations were conducted on all animals prior to the initiation of treatment and again prior to terminal sacrifice.

5. **Hematology and clinical chemistry:** Blood and urine samples were collected from all animals once during the pretest and prior to the terminal sacrifice. Bone marrow samples were also collected at terminal sacrifice. Animals were fasted overnight prior to sample collection. The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpuscle. HGB conc. (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpuscle. volume (MCV)*
X	Platelet count*		Reticulocyte count (Absolute)
	Blood clotting measurements*	X	Blood cell morphology
X	(Thromboplastin time [APTT])		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

b. Clinical chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Globulin*
	Magnesium	X	Creatinine*
X	Inorganic phosphorus	X	Urea nitrogen*
X	Potassium*	X	Total Cholesterol*
X	Sodium*	X	Albumin/Globulin ratio
	ENZYMES (more than 2 hepatic enzymes eg. *)	X	Glucose*
X	Alkaline phosphatase (ALK/also ALP))*	X	Total bilirubin
	Cholinesterase (ChE)		Total protein (TP)*
	Creatine phosphokinase	X	Triglycerides
	Lactic acid dehydrogenase (LDH)	X	Bile acid
X	Alanine aminotransferase (ALT/also SGPT)*	X	Total bilirubin
X	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral non-rodent studies based on Guideline 870.3150

6. Urinalysis: The CHECKED (X) parameters were examined.

X	Appearance (color)*	X	Glucose
X	Volume*	X	Ketones
X	Specific gravity*	X	Bilirubin
X	pH*	X	Blood*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Optional for subchronic oral non- rodent studies

7. Sacrifice and pathology: All dogs were euthanized by anesthesia with sodium pentobarbital. Gross pathological examinations were performed on all animals. The CHECKED (X) tissues were collected and preserved in buffered 10% formalin, except for

the eye (including the optic nerve) and testes, which were fixed using a modified Davidson's fixative prior to placing them in formalin. A full complement of tissues and organs was collected from all animals in the control, 3000 ppm and 10000 ppm groups. The CHECKED (X) tissues from animals of the treated and control groups were sectioned, stained with H&E, and subjected to histopathological examination. Gross lesions from the 300 ppm group were also evaluated microscopically. The (XX) organs were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC. /HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*-Sciatic
X	Esophagus*	X	Bone marrow*	X	Spinal cord*
X	Stomach*	X	Lymph nodes*(Mandibular	X	Pituitary*
X	Duodenum*	X	and Mesenteric)	X	Eyes (optic nerve)*
X	Jejunum*	XX	Spleen*+	X	**GLANDULAR**
X	Ileum*	XX	Thymus*+	XX	Adrenal gland*+
X	Cecum*	X	**UROGENITAL**		Lacrimal gland
X	Colon*	XX	Kidneys*+	XX	Parathyroid*
X	Rectum*	X	Urinary bladder*/Ureters	XX	Thyroid
XX	Liver*+	XX	Testes*+		Coagulating glands
X	Gall bladder (not rat)*	XX	Epididymides*+	X	Mammary gland*
X	GALTb	X	Prostate*	X	OTHERS
X	Pancreas*	X	Seminal vesicles*	X	Skin*
X	**RESPIRATORY**	XX	Ovaries*+	X	Gross lesions*
X	Trachea*	XX	Oviducts		Target organs
X	Lung*/Bronchi	XX	Uterus*+	X	Skeletal muscles
X	Nasal tissue*	XX	Cervix	X	Sternum/femur/rib
X	Larynx*/Pharynx			X	Tibiofemoral joint

* Recommended for 90-day oral non- rodent studies based on Guideline 870.3150
aGut associated lymphoid tissue

II. RESULTS:

A. OBSERVATIONS:

1. Clinical/Neurobehavioral signs of toxicity: Clinical and neurobehavioral signs were observed in the 10000 ppm dose groups, and included decreased activity (2/2 males), feces few/absent 2/2 males, 2/2 females), inappetence (2/2 males and 2/2 females), loss of skin elasticity (2/2 males, 2/2 females), thin appearance (2/2 males and 2/2 females), eyelids partially/completely closed (1/2 males), skin cold to touch (1/2 males), watery faeces (2/2 males), isolated incidences of vomitus (2/2 males), and non-specific neurobehavioral signs.

All animals survived until study termination with the exception of one male from the 10000 ppm group. This male was euthanized *in extremis* on Day 24 based on low food consumption, severe body weight loss, and clinical signs that progressed over time.

Microscopically, the cause of death was determined to be a result of acute bacterial pneumonia and considered unrelated to treatment.

2. **Neurological Observations:** No neurobehavioral effects were noted at doses up to 3000 ppm. In the high-dose male euthanized on day 24, slight impairment of forelimb and hindlimb strength, piloerection, and salivation. Additional signs observed at 10,000 ppm included slight impairment of forelimb strength in two animals (one male and one female), slight impairment of hindlimb strength in one male, partial/slow constriction of pupils in one male, and lack of pupil constriction in one female.

B. BODY WEIGHT AND WEIGHT GAIN:

The body weight and total body weight gain of dogs treated with triflumezopyrim are shown in Table 2. Treatment-related effects on body weight were noted in both sexes at 10000 ppm, and to a lesser extent for males at 3000 ppm, when compared to controls. Animals at 10000 ppm continued to lose weight after the dietary concentrations were reduced, although the magnitude of body weight loss was generally less severe. Final absolute body weights for the 10000 ppm dose group were 15.1% and 17.4% lower than controls for males and females, respectively. Final absolute body weights for the 3000 ppm dose group, were decreased relative to the control animals, however, only by 8.5%.

Table 2. Average body weights of dogs during 28 days of treatment[a]

Dose (ppm)	Body weight (kg ± SD)			Total weight change (Day1-29)
	Day 1	Day 15	Day 29	kg
Males				
0	9.825 (±0.87)	9.975 (±1.35)	9.755 (±0.53)	-0.070
300	9.725 (±0.40)	9.705 (±0.32)	10.005 (±0.22)	0.280
3000	9.655 (±0.12)	9.185 (±0.11)	8.930 (± 0.34) (-8.5%)	-0.725
10000	10.090 (±0.55)	8.020 (± 0.61) (-19.6%)	8.280 (N/A) (-15.1%) [b,c]	-2.200
Females				
0	8.445 (±0.4)	8.235 (±0.33)	8.270 (±0.27)	-0.175
300	8.650 (±0.61)	8.875 (±0.90)	9.180 (±1.09)	0.530
3000	8.680 (±0.51)	8.285 (±0.57)	8.250 (± 0.48) (-0.2%)	-0.430
10000	8.650 (±0.08)	7.190 (± 0) (-12.7%)	6.835 (±0.45) (-17.4%)	-1.815

[a] Data from pages 25 and 26 of MRID 49382159
[b] Single animal survived after Day 24; [c] Decrease compared to control
[c] One animal euthanized *in extremis* before day 29, leaving only one animal in the given dose group; no SD calculated

C. FOOD CONSUMPTION/FOOD EFFICIENCY:

Food consumption and food efficiency data are summarized in Table 3. There was a treatment-related decrease in food consumption of males and females in the 3000 (32.3% and 11.1% for males and females, respectively) and 10000 ppm (77.3% and 63.7% decrease for

males and females, respectively) groups when compared to the control groups. Decreases in food efficiency generally paralleled decreases in body weight gain and absolute bodyweight.

Table 3. Mean Food consumption/food efficiency in dogs during 28 days of treatment[a]

Parameter	0 ppm (0 mg/kg/day)	300 ppm (6.08-8.18 mg/kg/day [M/F])	3000 ppm (49.52-67.07 mg/kg/day [M/F])	10000 ppm (55.10-145.04 mg/kg/day [M/F])
Males				
Food consumption (g/animal/day), Days 1-29	223.85 - -	201.07 (10.2%)[b]	151.59 (-32.3%)	50.79 (-77.3%)
Food efficiency (%), Days 1-29	-1.42	4.90	-19.04	-260.66
Females				
Food consumption (g/animal/day), Days 1-29	213.21 - -	243.75 (+14.3 %)	189.45 (-11.1 %)	77.39 (-63.7 %)
Food efficiency (%), Days 1-29	-2.79	8.07	-8.10	-85.36

[a]Data from page 27 of MRID 49382159
[b]Values in parenthesis indicate % increase or decrease compared to control; calculated by the reviewer

D. OPHTHALMOSCOPIC EXAMINATION:

There were no treatment-related ophthalmological findings.

E. BLOOD ANALYSES:

Hematology: There were no treatment-related effects on hematological or coagulation parameters at any dose level.

Clinical chemistry: Male and female dogs exposed to 10000 ppm of triflumezopyrim exhibited mild hepatic effects and/or dysfunction as illustrated by mild increases in ALT (171%/162% [M/F]) and cholesterol (males only) (63.2%). The females at this concentration also exhibited mild decreases in total protein (11.6%) and albumin (10%). Both sexes also showed decreases in ALP (30%/48% [M/F]).

Unscheduled samples obtained from one male at 10000 ppm prior to euthanasia *in extremis* exhibited moderately elevated bile acids, ALT, aspartate aminotransferase, and minimally increased gamma glutamyltransferase, all which could be consistent with liver injury, but were thought to be caused by the bacterial pneumonia infection. Albumin and calcium were also slightly decreased in this individual, which is consistent with inflammation.

Given the lack of histopathological changes or changes in gross organ weight, these effects

are likely to be either non-specific indications of inflammation due to adaptive response to exposure of a xenobiotic. Therefore, these chemical changes were not judged to be adverse.

F. URINALYSIS: There were no treatment-related differences in urine parameters between the control and treated group for either sex.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** There were no treatment-related changes in mean organ weights. Observed differences in organ weight in the 10000 ppm group were minimal and were therefore judged to be incidental to the overall body weight loss.

2. **Gross pathology:** There were no treatment-related differences in gross pathology observed at necropsy.

   Microscopic pathology: There were no treatment-related microscopic observations in animals at doses up to 3000 ppm. At 10000 ppm, treatment-related microscopic findings were present in multiple organs, including testes/epididymides, skeletal muscle, salivary glands, thymus, kidneys (females only), and liver (females only). These included the following: 1) Minimal bilateral degeneration of spermatocytes/spermatids in seminiferous tubules of the testes and bilateral oligospermia/germ cell debris in the epididymides in one male at 10000 ppm; degenerative changes in germ cells of the testes may be the result of delayed maturation secondary to decreased food consumption and body weight loss. 2) Atrophy of the myofibers in the biceps femoris muscle in the male and females at 10000 ppm; 3) Atrophy of the salivary glands (mandibular, parotid, and sublingual) in the male and females at 10000 ppm; 4) Unilateral dilation/inflammation of the sublingual gland duct in one male at 10000 ppm; 5) An increased severity of decreased lymphocytes in the thymus in the male and females at 10000 ppm; 6) fatty change in tubules of the kidneys and fatty change in the liver in females at 10000 ppm both of which possibly associated with body weight loss and altered fat mobilization. This study was limited to only 2 dogs/sex/dose; however, studies of longer duration in dogs that were conducted according to guideline requirements are available (MRID 49382163 and MRID 49382164) and these effects were not observed. As a result, based on the weight of evidence, these effects were not considered treatment-related.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATOR' CONCLUSIONS:

The study authors concluded that dietary administration of Triflumezopyrim to Beagle dogs over 28 days produced treatment-related effects at ≥3000 ppm in both sexes. No effects were observed in 300 ppm males and females. All animals survived until study termination with the exception of one high-dose male, found moribund, died of bacterial pneumonia. Treatment-related reduction in body weight and nutritional parameters were observed in females at 3000 ppm and in both sexes at 10000 ppm compared to controls.

Treatment-related clinical observations were primarily noted in the 10000 ppm males and/or females, and included decreased activity, thin appearance, inappetence, effects on feces, loss of skin elasticity, eyelids partially/completely closed, and cold skin. There were no treatment-related effects on hematology, coagulation, clinical chemistry or urinalysis parameters. At termination in both sexes receiving 10000 ppm there was evidence of mild hepatic effects and or dysfunction as illustrated by mild decreases in total protein and albumin. These findings were considered treatment-related but possibly associated with body weight loss and changes in nutritional parameters. There were no treatment-related gross observations or organ weight changes.

At 10000 ppm, the microscopic findings, likely associated with severe body weight loss and/or nonspecific toxicity (stress), were present in multiple organs, including testes/epididymides, skeletal muscle, salivary glands, thymus, kidneys (females only), and liver (females only) and were considered adverse. Fatty change in tubules of the kidneys and in the liver of females at 10000 ppm were likely associated with body weight loss and altered fat mobilization. There were no treatment-related microscopic findings in animals at ≤.3000 ppm.

The NOAEL for males and females was 300 ppm (6.08 mg/kg bw/day for males and 8.18 mg/kg bw/day for females). This NOAEL was based on effects on body weight and nutritional parameters in dogs at the LOAEL, 3000 ppm (49.52 mg/kg bw/day for males and 67.07 mg/kg bw/day for females). The 10000 ppm concentration was considered to have exceeded the maximum tolerated dose.

B. REVIEWERS' COMMENTS:

Twenty-eight-day dietary treatment of Beagle dogs with triflumezopyrim produced adverse effects at 10000 ppm in both sexes. Treatment-related decreases in body weight and body weight gain were noted in males and in females at ≥3000 ppm, when compared to controls however, the magnitude of the absolute bodyweight change did not rise to the level of being considered an adverse effect (>10%). Changes in absolute bodyweight greater than 10% were noted in both sexes at the dose level of 10000 ppm.

There were no treatment-related effects on ophthalmoscopy, hematology, coagulation parameters, or urinalysis parameters at doses up to 3000 ppm (49.52/67.07 mg/kg/day [M/F]). For both sexes, there were mild increases in alanine aminotransferase and bile acids and decreases in total protein and albumin at 10000 ppm (55.10/145.04 mg/kg/day [M/F]). There were no treatment-related changes in organ weights, gross and microscopic pathology, or signs of specific target organ toxicity.

The NOAEL was 3000 ppm for male and female dogs (49.52 mg/kg/day for males and 67.07 mg/kg/day, for females).

The LOAEL was established at 10000 ppm for both sexes (55.10 mg/kg/day for males and 145.04 mg/kg/day for females) based on reductions in absolute body weight.

This 28-day oral toxicity study in the dogs is a range-finding study that was conducted for the purpose of setting doses for the follow-on studies. It **does not satisfy** any guideline requirements.

STUDY DEFICIENCIES:

- Small sample size (2 animals/sex/dose)
- Animals chosen were older than 9 months at study start date
- The overall dosing duration was only 28 days instead of the standard 90